REMARKS

Applicants respectfully request entry of the amendment and reconsideration of the claims. Claims 13-25 have been cancelled without prejudice. Claims 1-4 and 7 have amended to further clarify the claimed invention. The Office Action indicated claims 6 and 8 would be allowable if rewritten in independent form including all the limitations of the base claim and any intervening claims. Claims 6 and 8 have been rewritten into independent form as suggested by the Office Action. Applicants submit the amendment places the claims in condition for allowance. After entry of the amendment, claims 1-4 and 6-25 will be pending. Claims 13-25 have been withdrawn from consideration by the Examiner.

Co-pending Applications

Applicants note U.S. Patent Application Nos. 09/997,384, filed on November 15, 2001, and 09/997,601, filed on November 15, 2001, are co-pending.

Enablement

Claims 1-4, 7, 9-10, and 12 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. Applicants respectfully traverse this rejection.

In order to advance prosecution, claim 1 has been amended to encompass an isolated EG-VEGF polypeptide having at least 80% amino acid sequence identity with the amino acid sequence of residues 20-105 of SEQ ID NO:2. The language of the claim, which is consistent with the description in the specification (e.g., at page 13, lines 10-13), specifies that the claimed polypeptide contains the amino acid sequence of mature EG-VEGF (residues 20-105 of SEQ ID NO:2 or a sequence having at least 80% identity to residues 20-105). The claims also require that the isolated polypeptide promotes proliferation of ACE endothelial cells. As discussed below, the working examples demonstrate that EG-VEGF polypeptides induce proliferation of ACE cells.

As an initial matter, Applicants wish to clarify the definition of "EG-VEGF variant polypeptide" as clearly described in the specification. On page 13, "EG-VEGF variant polypeptide" is defined as an active EG-VEGF polypeptide having at least about 80% amino acid sequence identity with the amino acid sequence of

(a) residues 1 **or** about 20 to 105 of SEQ ID NO:2,

(b) X to 105 of SEQ ID NO:2 wherein X is any amino acid residue from 14 or 24 of SEQ ID NO:2, **or**

(c) another specifically derived fragment of the amino acid sequence of SEQ ID NO:2. As such, one of ordinary skill in the art reading this definition would understand that EG-VEGF variant polypeptides as described in the application fall into three different, albeit related categories. Comparing this definition to the presently amended claim 1, it is apparent that the presently amended claim 1 is directed to a part of category (a) under this definition (EG-VEGF variants having at least 80% amino acid sequence identity with the amino acid sequence of residues 20-105 of SEQ ID NO:2). In contrast, the Examiner's reading of claim 1 appears to rely on category (b) or (c) of the definition.

The Office Action acknowledges that the specification enables an isolated polypeptide comprising amino acid residues 20-105 of SEQ ID NO:2 (SEQ ID NO:2). The Office Action, however, asserts the specification does not enable claims to an isolated polypeptide that promotes proliferation of ACE cells and comprises an amino acid sequence having at least about 80%, 85%, 90%, 95%, or 100% identity to amino acid residues 20 to 105 of SEQ ID NO:2. Applicants respectfully do not agree.

Citing Ngo et al., Attwood et al., and Skolnick et al., the Office Action alleges the relationship between an amino acid sequence and its activity is unpredictable and that current sequence based methods for predicting structure and function are inadequate and unreliable.

Brenner et al., however, discloses that % sequence identity comparison methods are adequate and useful for predicting shared function (Brenner et al., 1998, *Science*, 95:6073-6078). Brenner et al. extracted the sequences of domains of proteins in the Protein Data Bank creating a database of domains that were used to assess sequence comparison methods. Using this database, Brenner et al. found that pairwise sequence comparison methods are capable of detecting almost all relationships between proteins whose sequence identities are greater than 30% (Brenner et al., Abstract at page 6073 and figure 3 at page 6075). Pairwise sequence comparison methods that utilized statistical scores, such as E-values, recognized greater than 90% of the homologous pairs with 30-40% identity (Brenner et al. at page 6077) leading Brenner et al. to conclude that E-values give fairly accurate estimates of the significance of pairwise

sequence matches and that the homologous proteins found by sequence comparison can be distinguished with high reliability from the huge number of unrelated pairs. (Brenner et al. at pages 6077-6078). The Brenner et al. study validated the use of sequence comparison methods to establish that % sequence identity comparisons greater than 30% are predictive of shared function.

In addition, angiogenic factors, such as VEGF, were known to exist in families having high amino acid sequence identity. See, for example, Tables 1 and 2 in the prior response. As discussed in the prior response, the post filing publications of LeCouter et al., Masuda et al., and Kisliouk et al. confirm that SEQ ID NO:2 is a member of a family having high amino acid sequence identity. Mature mouse, rat, and bovine EG-VEGF have at least 88% amino acid sequence identity with mature human EG-VEGF (residues 20-105 of SEQ ID NO:2). See Table 1 in the prior response. Therefore, one of skill in the art would have reasonably expected EG-VEGF, an angiogenic factor, to be a member of a protein family (including variants and homologs) having high amino acid sequence identity.

Citing Mikayama et al., the Office Action alleges a single amino acid change can have dramatic effects on a protein's function. Bowie et al., however, disclose that proteins are surprisingly tolerant of amino acid substitutions (Bowie et al., 1990, *Science*, 247:1306-1310 (copy enclosed in previous response)). In addition, the Office Action has not provided any evidence that a single amino acid change to an angiogenic factor, such as EG-VEGF, would completely destroy its activity.

Applicants further submit the specification provides adequate description of how to make and use the claimed EG-VEGF polypeptides. The Office Action alleges the specification lacks an *in vivo* working example demonstrating the EG-VEGF could treat any disease and that recent failures in clinical trails using VEGF antagonists indicate the unpredictability of angiogenesis inhibitors for treating disease, such as cancer. Applicants do not understand the relevancy of the disease treating ability to the presently claimed invention. The claims currently under examination are drawn to EG-VEGF polypeptides. The polypeptides are not defined in the pending claims by treating a disease but by a biological activity demonstrated in the working examples.

Any enabled use that reasonably correlates with the scope of the claim is sufficient to preclude a rejection for nonenablement. MPEP § 2164.02. The working examples in the specification demonstrate at least two uses for EG-VEGF polypeptides: inducing endothelial cell proliferation and/or angiogenesis. Example 14 demonstrates that EG-VEGF polypeptides induce proliferation of endothelial cells *in vitro*. As shown in Figure 13 and described in Example 14, EG-VEGF stimulated proliferation of ACE cells and induced a fold increase in cell number similar to that induced by VEGF. Example 20 demonstrates that EG-VEGF induces angiogenesis *in vivo*. Intra-ovarian delivery of a recombinant adenoviral vector expressing EG-VEGF resulted in a strong angiogenic response in the ovarian tissue similar to the angiogenic response induced by administration of an adenoviral vector expressing VEGF (Figure 19, panel i).

In contrast to the Examiner's opinions regarding VEGF antagonists, the VEGF antagonist bevaczimuab has been approved by the FDA for the treatment of cancer (see press release enclosed with previous response).

The Office Action also alleges the specification does not teach any assays that are useful for screening variants. Applicants respectfully do not agree.

One of skill in the art is fully enabled to identify EG-VEGF variants without undue experimentation, for example, using the EST techniques, hybridization probes, or anti-EG-VEGF antibodies described in the specification. The EST, hybridization, and antibody assays described in the specification are well known in the art. The Examiner has not shown that undue experimentation would be required to use these methods. Applicants' post filing publication, in which mouse EG-VEGF was identified using an EST highly related to human EG-VEGF, confirms the teachings of the specification. See LeCouter et al., 2003, *Endocrinology*, 144:2606-2616. Mouse EG-VEGF has 88% identity to amino acid residues 20-105 of SEQ ID NO:2 and induces proliferation of ACE cells (see Figures 1B and 7A in LeCouter et al.).

Furthermore, as discussed above, the specification teaches different ways to determine whether an isolated EG-VEGF polypeptide sharing high percentage of sequence identity to the full length or mature form of the native EG-VEGF (SEQ ID NO:2) is capable of promoting proliferation of adrenal cortex-derived capillary endothelial cells. For example, Example 14 describes how to screen EG-VEGF polypeptides for ACE cell proliferation activity.

For the reasons discussed above, Applicants submit the specification fully enables the claims. Applicants assert the guidance and examples provided in the specification are sufficient to enable one of skill in the art to make and use the claimed EG-VEGF polypeptides without undue experimentation. Withdrawal of the rejection is respectfully requested.

Written Description

Claims 1-4, 7, 9-10, and 12 were rejected under 35 U.S.C. § 112, first paragraph, as lacking written description. Applicants respectfully traverse this rejection.

The Office Action asserts the specification does not adequately describe an isolated polypeptide comprising an amino acid sequence having at least about 80%, 85%, 90%, 95%, or 100% identity to amino acid residues 20 to 105 of SEQ ID NO:2 that promotes proliferation of ACE cells. Applicants respectfully do not agree.

In order to advance prosecution, claim 1 as amended is drawn to an isolated EG-VEGF polypeptide having at least 80% amino acid sequence identity with the amino acid sequence of residues 20-105 of SEQ ID NO:2. The language of the claim is consistent with the description of EG-VEGF in the specification (e.g., at page 13, lines 10-13) and specifies that the claimed polypeptide contains the amino acid sequence of mature EG-VEGF (residues 20-105 of SEQ ID NO:2 or a sequence having at least 80% identity to residues 20-105).

EG-VEGF polypeptides having at least 80% amino acid sequence identity with the amino acid sequence of residues 20-105 of SEQ ID NO:2 are clearly described in the specification. On page 13, "EG-VEGF variant polypeptide" is described as an active EG-VEGF polypeptide having at least about 80% amino acid sequence identity with the amino acid sequence of

(a) residues 1 **or** about 20 to 105 of SEQ ID NO:2,

(b) X to 105 of SEQ ID NO:2 wherein X is any amino acid residue from 14 or 24 of SEQ ID NO:2, **or**

(c) another specifically derived fragment of the amino acid sequence of SEQ ID NO:2.

As such, one of ordinary skill in the art reading this definition would understand that EG-VEGF variant polypeptides as described in the application fall into three different, albeit related categories. Comparing this definition to the presently amended claim 1, it is apparent that the presently amended claim 1 is directed to a part of category (a) under this definition (EG-VEGF

variants having at least 80% amino acid sequence identity with the amino acid sequence of residues 20-105 of SEQ ID NO:2). In contrast, the Examiner's reading of claim 1 appears to rely on category (b) or (c) of the definition.

On page 45, the specification describes variants of EG-VEGF to include EG-VEGF derived from other species. Also described are nucleic acid probes derived from EG-VEGF useful to identify such variant species. As discussed in the prior response, non-human species of EG-VEGF having at least 80% amino acid sequence identity with the amino acid sequence of residues 20-105 of SEQ ID NO:2 were identified for murine, rat, and bovine species (see Table 1 of the prior response).

As described in Example 14, EG-VEGF induced proliferation of ACE cells as did the angiogenic factor VEGF. Further, Example 20 demonstrates that like VEGF, EG-VEGF induced angiogenesis in ovarian tissue. As discussed in the prior response, angiogenic factors like VEGF were known to exist in protein families having high amino acid identity. Like VEGF and its variants, EG-VEGF is described in the specification, for example, at page 13 to include active EG-VEGF variants having at least 80% amino acid sequence identity with amino acid sequence of residues 20 to 105 of SEQ ID NO:2. As discussed above, active EG-VEGF variants having at least 80% amino acid sequence identity with the amino acid sequence of residues 20-105 of SEQ ID NO:2 were identified for murine, rat, and bovine species (see Table 1 of the prior response).

For at least these reasons, Applicants respectfully submit the specification fully describes the claimed invention. Removal of the written description rejection is respectfully requested.

Summary

In view of the above amendments and remarks, Applicants respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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